EXHIBIT A

2002

USP 25

THE UNITED STATES PHARMACOPEIA

NF 20

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., April 12–16, 2000. Prepared by the Council of Experts and published by the Board of Trustees

Official from January 1, 2002

The designation on the cover of this publication, "USP NF 2002," is for ease of identification only. The publication contains two separate compendia: The Pharmacopeia of the United States Twenty-fifth Revision, and the National Formulary, Twentieth Edition.

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

Excipients

USP and NF Excipients, Listed by Categories

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Citric Acid
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

Aerosol Propellant
Butane
Dichlorodifluoromethane
Dichlorotetrafluoroethane
Isobutane
Propane
Trichloromonofluoromethane

Air Displacement
Carbon Dioxide
Nitrogen

Alcohol Denaturant
Denatonium Benzoate
Methyl Isobutyl Ketone
Sucrose Octacetate

Alkalizing Agent
Ammonia Solution, Strong
Ammonium Carbonate
Diethanolamine
Potassium Hydroxide
Sodium Bicarbonate
Sodium Borate
Sodium Carbonate
Sodium Hydroxide
Trolamine

Anticaking Agent (See *Glidant*)

Antifoaming Agent
Dimethicone
Simethicone

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

Antioxidant
Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Butylated Hydroxytoluene
Hypophosphorous Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Sodium Formaldehyde Sulfoxylate
Sodium Metabisulfite
Sodium Thiosulfate
Sulfur Dioxide
Tocopherol
Tocopherols Excipient

Buffering Agent
Acetic Acid
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
Citric Acid
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic

Bulking Agent for Freeze-Drying
Creatinine
Mannitol

Capsule Lubricant (See *Tablet and/or Capsule Lubricant*)

Chelating Agent
Edetate Calcium Disodium
Edetate Disodium
Edetic Acid

Coating Agent
Carboxymethylcellulose, Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Phthalate (see Cellacefate)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer

Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Color

Caramel
Ferric Oxide, red yellow, black, or blends

Complexing Agent

Edetate Disodium
Edetic Acid
Oxyquinoline Sulfate

Desiccant

Calcium Chloride
Calcium Sulfate
Silicon Dioxide

Emollient

Alkyl (C12-15) Benzoate

Emulsifying and/or Solubilizing Agent

Acacia
Cholesterol
Diethanolamine (Adjunct)
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying

Filtering Aid

Cellulose, Powdered
Siliceous Earth, Purified

Flavors and Perfumes

Anethole
Benzaldehyde
Ethyl Vanillin
Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

Glidant and/or Anticaking Agent

Calcium Silicate
Magnesium Silicate
Silicon Dioxide, Colloidal
Talc

Humectant

Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol

Ointment Base

Diethylene Glycol Monoethyl Ether
Lanolin
Ointment, Hydrophilic
Ointment, White
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane
Vegetable Oil, Hydrogenated, Type II

Plasticizer

Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol
Triacetin
Tributyl Citrate
Triethyl Citrate

Polymer Membrane

Cellulose Acetate

Sequestering Agent

Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

Solvent

Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Sorbent

Cellulose, Powdered
Charcoal
Siliceous Earth, Purified

Sorbent, Carbon Dioxide

Barium Hydroxide Lime
Soda Lime

Stiffening Agent

Castor Oil, Hydrogenated

Cetostearyl Alcohol
Cetyl Alcohol
Cetyl Esters Wax
Cetyl Palmitate
Hard Fat
Paraffin
Synthetic Paraffin
Stearyl Alcohol
Wax, Emulsifying
Wax, White
Wax, Yellow

Suppository Base

Cocoa Butter
Hard Fat
Polyethylene Glycol

Suspending and/or Viscosity-increasing Agent

Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
Dextrin
Gelatin
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Tragacanth
Xanthan Gum

Sweetening Agent

Aspartame
Dextrates
Dextrose
Dextrose Excipient
Fructose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

Tablet Binder

Acacia
Alginic Acid
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Hydroxypropyl Methylcellulose
Methylcellulose
Polyethylene Oxide
Povidone
Starch, Pregelatinized
Syrup

Tablet and/or Capsule Diluent

Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose
Mannitol
Sorbitol
Starch
Starch, Pregelatinized
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Tablet Disintegrant

Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone
Polacrilin Potassium
Sodium Starch Glycolate
Starch
Starch, Pregelatinized

Tablet and/or Capsule Lubricant

Calcium Stearate
Glyceryl Behenate
Magnesium Stearate
Mineral Oil, Light
Polyethylene Glycol
Sodium Stearyl Fumarate
Stearic Acid
Stearic Acid, Purified
Talc
Vegetable Oil, Hydrogenated, Type I
Zinc Stearate

Tonicity Agent

Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Vehicle

FLAVORED AND/OR SWEETENED

Aromatic Elixir
Benzaldehyde Elixir, Compound
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS

Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil

Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane

SOLID CARRIER
Sugar Spheres

STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

Viscosity-Increasing (See *Suspending Agent*)

Water Repelling Agent
Cyclomethicone
Dimethicone
Simethicone

Wetting and/or Solubilizing Agent
Benzalkonium Chloride
Benzethonium Chloride
Cetylpyridinium Chloride
Docusate Sodium
Nonoxynol 9
Octoxynol 9
Poloxamer
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium Lauryl Sulfate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Tyloxapol

EXHIBIT B

21ST EDITION

Remington

The Science and Practice of Pharmacy

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Editor: David B. Troy
Managing Editor: Matthew J. Hauber
Marketing Manager: Marisa A. O'Brien

Lippincott Williams & Wilkins

351 West Camden Street
Baltimore, Maryland 21201-2436 USA

530 Walnut Street
Philadelphia, PA 19106

Printed in the United States of America

Entered according to Act of Congress, in the year 1885 by Joseph P Remington, in the Office of the Librarian of Congress, at Washington DC

Library of Congress Catalog Card Information is available
ISBN 0-7817-4673-6

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2 3 4 5 6 7 8 9 10

of colored syrups causes the previously dried coating layers to be redissolved. Rough tablet surfaces will produce a *marbled* appearance during polishing, since wax buildup occurs in the small depressions in the tablet surface.

Film Coating of Solid Dosage Forms

Film coating is a process that involves the deposition of a thin, but uniform, film onto the surface of the substrate. Unlike sugar coating, film coating is a very flexible process that allows a broad range of products (eg, tablets, powders, granules, nonpareils, capsules) to be coated. Film coatings essentially are typically applied continuously to a moving mass of product, usually by means of a spray technique, although manual application procedures have been used.

Historically, film coating was introduced in the early 1950s to combat the shortcomings of the then predominant sugar-coating process. Film coating has proved successful as a result of the many advantages offered, including

1. Minimal weight increase (typically 2–3% of tablet core weight)
2. Significant reduction in processing times
3. Increased process efficiency and output
4. Increased flexibility in formulations
5. Improved resistance to chipping of the coating

In the early years of film coating, the major process advantages resulted from the greater volatility of the organic solvents used; however, the use of such organic solvents has created many potential problems, including

1. Flammability hazards
2. Toxicity hazards
3. Concerns over environmental pollution
4. Cost (relating either to minimizing items 1 to 3 or to the cost of the solvents themselves)

However, since the initial introduction of film coating, significant advances have been made in process technology and equipment design. The emphasis has changed from a process needing highly volatile organic solvents (in order to facilitate rapid drying) to one where even a relatively slow drying solvent such as water can be accommodated through significant improvements in the drying capabilities of the processing equipment used.

Thus, there has been a transition from conventional pans to side-vented pans and fluid-bed equipment, and consequently from the problematic organic solvent-based process to an aqueous one.

FILM COATING RAW MATERIALS—The major components in any film-coating formulation consist primarily of a polymer, plasticizer, colorant, and solvent (or vehicle).

Ideal properties for the polymer include solubility in a wide range of solvent systems to promote flexibility in formulation, an ability to produce coatings that have suitable mechanical properties, and appropriate solubility in gastrointestinal fluids such that drug bioavailability is not compromised.

Cellulose ethers are often the preferred polymers in film coating, particularly hydroxypropyl methylcellulose. Suitable substitutes are hydroxypropyl cellulose, which may produce slightly tackier coatings, and methylcellulose, although this polymer has been reported to retard drug dissolution.[10] Alternatives to the cellulose ethers are acrylic copolymers (eg, methacrylate and methyl methacrylate copolymers) and vinyl polymers (eg, polyvinyl alcohol).

For most film-coating applications, where there is no intent to modify drug-release characteristics, polymers are typically used as solutions in either water (preferred) or organic solvents.

Many of the commonly used polymers are available in a range of molecular-weight grades, a factor that also must be considered in the selection process. Molecular weight may have an important influence on various properties of the coating system, such as solution viscosity and mechanical strength and flexibility of the resultant film.

The incorporation of a plasticizer into the formulation improves the flexibility of the coating, reduces the risk of the film cracking, and potentially improves adhesion of the film to the substrate. To ensure that these benefits are achieved, the plasticizer must show a high degree of compatibility with the polymer and be retained permanently in the film, if the properties of the coating are to remain consistent on storage. Examples of typical plasticizers include glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglyceride, citrate esters (eg, triethyl citrate), or phthalate esters (eg, diethyl phthalate).

Colorants usually are used to improve the appearance of the product as well as to facilitate product identification. Additionally, certain physical properties of the coating (eg, its performance as a moisture barrier) may be improved. As in the case of sugar coating, colorants can be classified as either water-soluble dyes or insoluble pigments.

The use of water-soluble dyes is precluded with organic solvent-based film coating because of the lack of solubility in the solvent system. Thus, the use of pigments, particularly aluminum lakes, provides the most useful means of coloring film-coating systems. Although it may seem obvious to use water-soluble dyes in aqueous formulations, the use of pigments is preferred, since:

1. They are unlikely to interfere with bioavailability[11] as do some water-soluble dyes.
2. They help to reduce the permeability of the coating to moisture.[12]
3. They serve as bulking agents to increase the overall solids content in the coating dispersion without dramatically increasing viscosity.
4. They tend to be more light stable.

The major solvents used in film coating typically belong to one of these classes: alcohols, ketones, esters, chlorinated hydrocarbons, and water. Solvents perform an important function in the film-coating process, since they aid in the application of the coating to the surface of the substrate. Good interaction between solvent and polymer is necessary to ensure that optimal film properties are obtained when the coating dries. This initial interaction between solvent and polymer will yield maximum polymer chain extension, producing films having the greatest cohesive strength and, thus, the best mechanical properties. An important function of the solvent systems also is to ensure a controlled deposition of the polymer onto the surface of the substrate so that a coherent and adherent film coat is obtained.

Although it is very difficult to give typical examples of film-coating formulations, since these will depend on the properties of the materials used, such formulations usually are based on 5–20% (w/w) coating solids in the requisite vehicle (with the higher concentration range preferred for aqueous formulations), of which 60–70% is polymer, 6–7% is plasticizer, and 20–30% is pigment.

Modified-Release Film Coatings

Film coatings can be applied to pharmaceutical products to modify drug release. The USP describes two types of modified-release dosage forms, namely those that are *delayed release* and those that are *extended release*. Delayed-release products often are designed to prevent drug release in the upper part of the gastrointestinal (GI) tract. Film coatings used to prepare this type of dosage form are commonly called *enteric coatings*. Extended-release products are designed to extend drug release over a period of time, a result that can be achieved by the application of a *sustained-* or *controlled-release* film coating.

ENTERIC COATINGS—Enteric coatings generally remain intact in the stomach but will dissolve and release the contents of the dosage form once it reaches the small intestine. The purpose of an enteric coating is to delay the release of drugs that are inactivated by the stomach contents, (eg, pancreatin, erythromycin, and substituted benzimidazole compounds that are proton pump inhibitors) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). In addition, such coatings can be used to give a simple repeat-action effect